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TETRAHEDRON: *ASYMMETRY*

The synthesis of L-(+)-homophenylalanine hydrochloride

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Abstract

L-(+)-Homophenylalanine hydrochloride was synthesized from *N*-phthaloyl-L-(–)-aspartic anhydride **2** in three steps in 55% overall yield with 99% ee.

1. Introduction

α-Amino acids take an important role in biology because many of them are the precursors for a variety of biologically active compounds.[1,2] Among them, L-(+)-homophenylalanine [L-(+)-HPA] has received great attention because of its pharmaceutical interest as a component of ACE-inhibitors. Although many methods have been reported for the preparation of L-(+)-HPA, most of them are not economical enough for practical purposes.[3] For example, L-(+)-HPA was synthesized in four steps from α-*t*-butyl, β-methyl ester of *N*-benzyloxycarbonyl-(*S*)-aspartate in 13% overall yield with 80% ee.[4] Herein, we describe a method of the synthesis of L-(+)-HPA hydrochloride using *N*-phthaloyl-L-(–)-aspartic anhydride as starting material in three steps in 55% overall yield with 99% ee.

2. Results and discussion

The synthetic route for compound **1** is summarized in Scheme 1. *N*-Phthaloyl-L-(–)-aspartic anhydride **2** was prepared according to the literature.[5] The following Friedel–Crafts acylation of benzene with **2** had been reported by Dornhege et al.[5] to give **5** based on the ^{1}H NMR spectra, however, we found that **3** is the authentic product in the reaction (Scheme 2).

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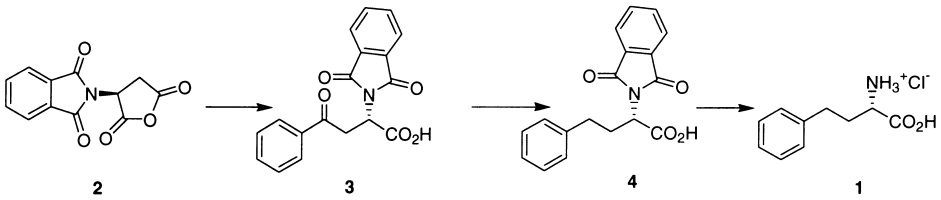
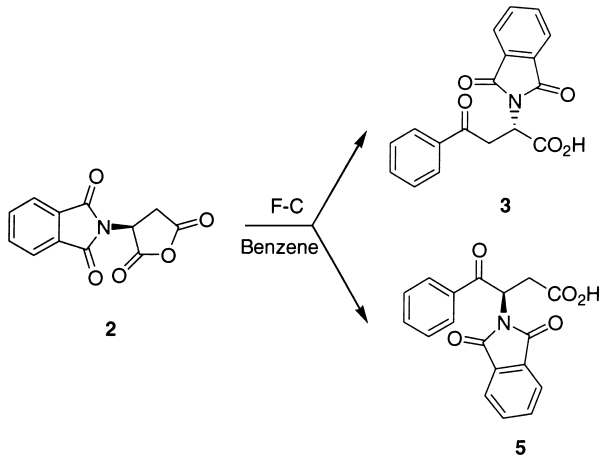


Scheme 1. *Reagents and conditions:* (a) $AlCl_3$, benzene, 50°C, 3 h, 79%; (b) H_2, 10% Pd/C, HOAc, 50°C, 3 h, 92%; (c) HOAc/6N HCl (v:v = 5:2), reflux, 6–8 h, 75%

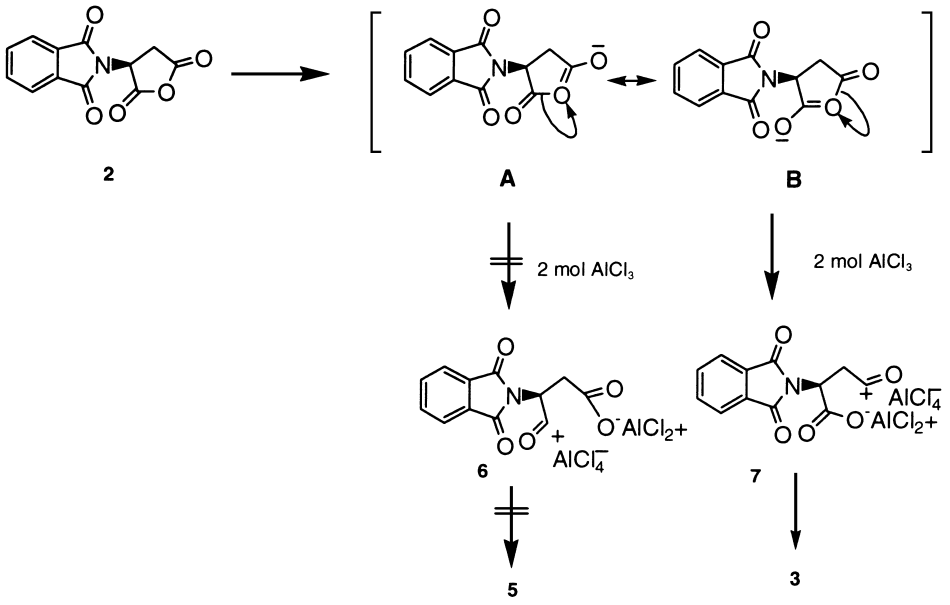


Scheme 2.

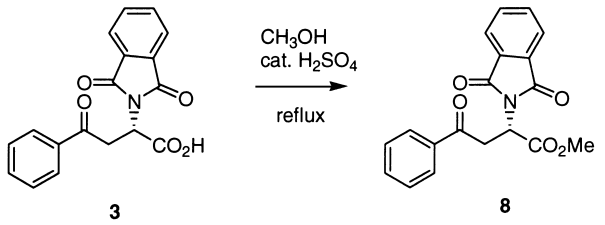
This result can be explained by the possible mechanism shown in Scheme 3. As can be seen from the two canonical structures A and B of **2**, the lone pair electrons of the center oxygen were competed for by two carbonyl groups. The resonance form B is more favored because the *N*-phthaloylamino group has a stronger electron withdrawing effect to the α-carbonyl group. Therefore, the more favored intermediate **7** leads to **3** as the sole product in the Friedel–Crafts acylation reaction.

In order to confirm this conclusion, an X-ray study on the methyl ester of **3** (Scheme 4) was carried out (Fig. 1). The X-ray structure of **8** clearly indicates that **3** is the structure of the Friedel–Crafts product. It is understandable that an incorrect structure might be assigned based on the ambiguity of the NMR spectra between **3** and **5** [^{1}H NMR (CD_3COCD_3)[5] for **5**: 3.79 (q, 2H), 4.25 (q, 1H), 5.77 (q, 4H), 7.88 (m, 4H), 7.34–8.16 (m, 5H), 10.26 (s, 1H), which is essentially the same as that for **3** assigned by this report]. Although Dornhege's conclusion did not effect the synthesis of the optically active 2-amino-tetralin, on revision of the structure it became a practical methodology for the preparation of L-(+)-HPA.

Hydrogenolysis of **3** gave **4** in 92% yield, which was deprotected with 6N hydrogen chloride in acetic acid (v:v = 2:5) to afford **1** in 75% yield, whose spectral data were in agreement with the literature.[3a] In order to determine the ee of **1**, it was esterified with ethanolic hydrogen chloride as ethyl L-(+)-HPA and determined by HPLC to be 99% ee, and thus the ee of **1** would be 99%. The above conclusion on the regioselectivity of Friedel–Crafts acylation of **2** with benzene was further confirmed by the completed synthesis of **1**.



Scheme 3.



Scheme 4.

3. Conclusion

In brief, we have reported a practical method for the synthesis of L-(+)-HPA hydrochloride in good overall yield (55%) with an excellent enantiomeric excess (99%). This methodology should be adaptable to the synthesis of a variety of substituted homophenylalanines.

4. Experimental

4.1. General methods

Melting points were taken on a Kofler melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-80 NMR spectrometer with TMS as an internal reference for chemical shifts expressed as δ-values in ppm and coupling constants in hertz. Mass spectra were obtained on a Hewlett–Packard HP5988A mass spectrometer using EI ionization. IR spectra were recorded on a Nicolet FT-IR 170X spectrometer. Optical rotations were measured on a Jasco J-20C automatic polarimeter. Enantiomeric excess (ee) determination was carried out using

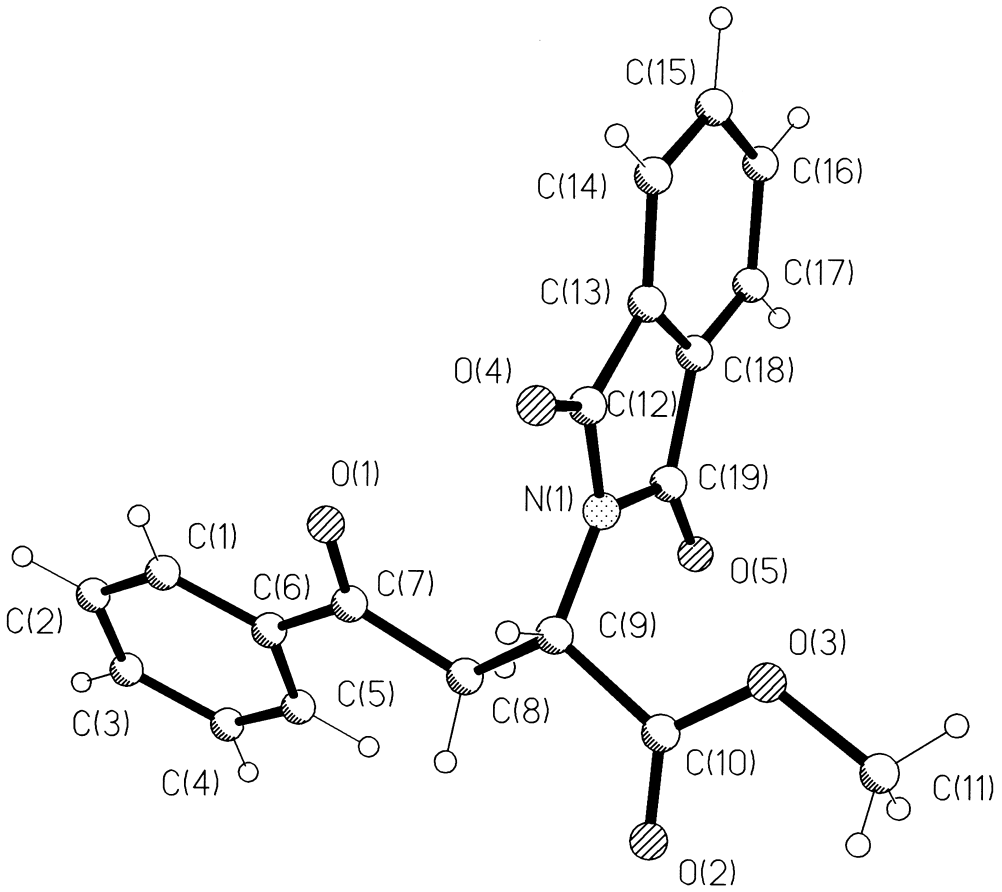


Figure 1. The X-ray structure of **8**

hexane:isopropyl alcohol (90:10, 1.0 mL/min) as eluent with a Chiralcel CDMPC (150×4.6 mm) column (Daicel Chemical Industries) on a Varian SD-200 HPLC instrument.

4.2. N-*Phthaloyl-L-(−)-4-oxo-homophenylalanine* ***3***

Compound **2** (1 mol) was added portionwise to a solution of 2.5 mol anhydrous $AlCl_3$ in 4.8 L benzene at room temperature. Then the mixture was heated to 50°C gradually and stirred for 3 h at that temperature. Cooling to rt, 2000 g crushed ice and 230 mL concentrated HCl were added with stirring. The precipitated product was filtered, washed with water, and dried in vacuo to afford **3** as white solid (79% yield). Mp 161–163°C; $[\alpha]_D^{20} = -15.0$ (*c*, 4.3, ethanol) [lit.[5] mp 165–167°C; $[\alpha]_D^{20} = -14.7$ (*c*, 5.0, ethanol)]; ^{1}H NMR (CD_3COCD_3): 3.90 (1H, dd, J = 6.7, 17.9, CH_2); 4.10 (1H, dd, J = 6.7, 17.9, CH_2); 5.71 (1H, m, CH); 7.45–7.67 (4H, m, Ar-H); 7.90 (5H, s, Ar-H); m/z (EI): 323 (2); 305 (34); 218 (18); 174 (7); 105 (100).

4.3. N-*Phthaloyl-L-(−)-homophenylalanine* ***4***

Compound **3** (1 mol) in 30 L acetic acid was hydrogenated over 10% Pd/C (46 g) for 3 h at normal pressure and 50°C. The catalyst was filtered off, and the filtrate was concentrated in

reduced pressure to 100 mL. Water was added until precipitate was produced, then the mixture was stored in a refrigerator overnight. The product was collected by filtration, washed with water, and dried in vacuo to give **4** as white solid (92% yield). Mp 140–142°C; $[\alpha]_D^{20} = -10.0$ (*c*, 4.0, ethanol); ^{1}H NMR ($CDCl_3$): 2.48–2.92 (4H, m, CH_2); 4.86–5.05 (1H, m, CH); 7.17 (5H, s, Ar-H); 7.63–7.93 (4H, m, Ar-H); 11.23 (1H, s, COOH); m/z (EI): 309 (1); 279 (1); 205(8); 187 (6); 148 (13); 91 (100).

4.4. L-(+)-Homophenylalanine hydrochloride *1*

To the solution of 1 mol **4** in 7.5 L acetic acid was added 3 L 6N HCl and the mixture was refluxed for 6–8 h. The acetic acid was then removed in reduced pressure and the residue was dissolved in 3 L 3N HCl with stirring. After that the solution was filtered. The filtrate was taken to dryness under reduced pressure, and the solid was collected by filtration and dried in vacuo to give **1** as white solid (75% yield). Mp 250–260°C; $[\alpha]_D^{20} = +40$ (*c*, 0.6, 3N HCl) [lit.[6] $[\alpha]_D^{20} = +45.0$ (*c*, 1.0, 3N HCl)]; IR (KBr, cm^{-1}): 3000 (NH_2), 1740 (CO). Anal. calcd for $C_{10}H_{13}NO_2 \cdot HCl$: C, 55.69; H, 6.54; N, 6.49. Found: C, 55.60; H, 6.62; N, 6.40. ^{1}H NMR (CF_3COOD): 2.63–2.79 (2H, m, CH_2); 3.09–3.18 (2H, t, J = 7.0, CH_2); 4.55 (1H, m, CH); 7.41 (5H, s, Ar-H); m/z (EI): 179 (2); 162 (10); 134 (24); 91 (100).

4.5. Methyl 2-N-phthaloyl-L-(−)-4-oxo-homophenylalanine *8*

Compound **3** (500 mg) was dissolved in 20 mL methanol with 0.2 mL concentrated H_2SO_4, and the resulting solution was refluxed until TLC indicated the reaction to be complete. Methanol was evaporated in vacuo, the residue was dissolved in saturated $NaHCO_3$ solution and extracted with ethyl acetate (15 mL×3). The combined organic solution was washed with brine, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue was recrystallized from ethanol to afford **8** as a white solid (90% yield). ^{1}H NMR ($CDCl_3$): 3.77 (3H, s, OCH_3); 3.91–4.21 (2H, m, CH_2); 5.66–5.83 (1H, dd, J = 5.8, 7.6, CH); 7.45 (5H, s, Ar-H); 7.68–8.05 (4H, m, Ar-H); m/z (EI): 337 (0.2), 305 (2), 105 (100).

X-Ray crystal data collection and refinement for **8**: formula, $C_{19}H_{15}NO_5$; Mr, 337.32. Crystal system, monoclinic; space group, $P2_1/n$; *a*, 8.586(4) Å; *b*, 17.284(2) Å; *c*, 11.449(3) Å; *V*, 1649.0(9) $Å^3$; *Z*, 4; D_c, 1.359 g cm^{-3}; *F*(000), 740; μ, 0.099 mm^{-1}; *T*, 20°C; independent reflections, 2891. Observed data with $I = 3\sigma(I)$, 1750; radiation (λ/Å), MoKα; scan type, $\omega/2\theta$; $2\theta_{max}$, 50°; *R*, 0.0256; R_w, 0.71073. Goodness-of-fit indicator, 1.140.

4.6. Determination of the ee of *1*

Amino acid **1** (~100 mg) was refluxed in EtOH·HCl (5 mL, 1N) until TLC indicated the starting material had disappeared. Ethanol was evaporated under reduced pressure, and the residue was purified as above to afford ethyl L-(+)-HPA. Chiral HPLC analysis shows ethyl L-(+)-HPA with 99% ee.

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